PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WO/348		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02490	27/04/1998	28/04/1997
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
APPLIED RESEARCH SYSTEMS ARS HOLDING N.V et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/11/1998	22.06.99
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Vollbach, S Telephone No. (+49-89) 2399 8715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/02490

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-70 as originally filed

Claims, No.:

1-31 as received on 14/05/1999 with letter of 11/05/1999

Drawings, sheets:

1/20-20/20 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 21-31.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 21-31 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,6
	No:	Claims	2-5,7-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,6,16-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. The present set of claims, in principle, comprises two groups of claims, namely those which are directed to the DNA sequence encoding the "GILR" protein, the corresponding protein and antibodies specific for said protein (Claims 1-14), and claims which are directed to medical uses of said protein and pharmaceutical compositions (claim 15-31).

As far as the first group is concerned, at least, in the present form, they are not new and/or inventive. In fact, the "GILR" protein which belong to the leucine zipper family" has a high degree of homology with other members of said family (see e.g. D1= J. Biol Chem, vol. 267 (15), Shibanuma et al., 1992; and D2= Biochem Biophys Res Commun, vol. 222 (3), Jay et al., 1996) respectively to proteins which are not known to belong to said family (See D3=EUR J Biochem, vol. 216 (2), Sillard et al. 1993). Therefore present claims 2-5,7-15 of said group insofar as they refer to "derivatives, parts sequences defined by the capability to hybridize to a specific DNA sequence" are not novel in view of D1-D3.
As far as the second group of claims is concerned several objections apply.
First, general applications or uses (i.e claims 15-20) cannot be regarded inventive since they are obvious in view of the known characteristics of the members of the leucine zipper family (D1-D2). Second with regard to more specific uses, it has to be mentioned that these specific uses are merely based on some preliminary results which are considered insufficient to proof that the protein indeed can be successfully applied for the indicated purposes. Therefore said claims are not sufficiently supported by experimental data in this respect, but are merely based on speculations. This clearly contravenes the requirements of Article 6 PCT.

2. Moreover, claim 15 is drafted in the form "use of protein GILR in the preparation of a medicament for inhibiting apoptosis". Most of the other claims merely refer to different forms of applying said protein or the DNA. Thus it is questionable whether said claims have any influence or relevance on the scope of "basic" claim 1.

CLAIMS

1. A DNA sequence comprising the DNA sequence SEQ ID NO: 1 and encoding a glucocorticoid-induced leucine-zipper family related protein (GILR).

2. A DNA sequence according to claim 1 selected from the group consisting of :

(a) a cDNA sequence derived from the coding region of a native GILR protein;

(b) DNA sequences capable of hybridization to a sequence of (a) under stringent conditions and which encode a biologically active GILR protein; and

(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (a) and (b) and which encode a biologically active GILR protein.

3. A DNA sequence according to claim 1 or claim 2 comprising at least part of the DNA sequence SEQ ID NO: 1 and encoding at least one active GILR protein.

4. A DNA sequence according to claim 3 encoding a GILR protein comprising the amino acid sequence SEQ ID NO: 2.

5. A DNA sequence according to claim 1 or claim 2 comprising at least part of the DNA sequence SEQ ID NO: 5 and encoding at least one active human GILR protein

6. A DNA sequence according to claim 5 encoding a human GILR protein comprising the amino acid sequence SEQ ID NO: 6.

7. A vector comprising a DNA sequence according to any one of claims 1-6.

8. A vector according to claim 7 capable of being expressed in a eukaryotic host cell.

9. A vector according to claim 7 capable of being expressed in a prokaryotic host cell.

10. Transformed eukaryotic or prokaryotic host cells containing a vector according to any one of claims 7-9.

11. A GILR protein or derivatives thereof encoded by a DNA sequence according to any one of claims 1-6, said protein and derivatives thereof being capable of inhibiting apoptosis and stimulating lymphocyte activity.

12. A GILR protein and derivatives thereof according to claim 11, wherein said protein and derivatives have at least part of the amino acid sequence SEQ ID NO: 2 or of the amino acid sequence SEQ ID NO: 5.

13. Process for the preparation the GILR protein or derivatives thereof according to claim 11 or 12, comprising growing the transformed host cells according to claim 12 under conditions suitable for the expression of said proteins, effecting post-translational modifications as necessary for obtaining of said protein or derivatives and isolating said expressed protein or derivatives.

14. Antibodies or active fragments or derivatives thereof, specific for the GILR protein or derivatives according to claim 11 or 12.

15. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for the inhibition of apoptosis in cells, mediated by the Fas/FasL system, CD3/TCR system or other intracellular mediators of apoptosis, comprising treating said cells with one or more GILR proteins or derivatives according to claim 11 or 12, wherein said treating of said cells comprises introducing into said cells said one or more proteins or derivatives in a form suitable for intracellular introduction thereof, or introducing into said cells a DNA sequence encoding said one or more proteins or derivatives in the form of a suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.

16. Use according to claim 15, wherein said treating of cells comprises introducing into said cells a DNA sequence encoding said GILR protein or derivatives in the form of a suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.

17. Use according to claim 15 or 16 wherein said treating of said cells is by transfection of said cells with a recombinant animal virus vector comprising the steps of :

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein (ligand) that is capable of binding to a specific cell surface receptor on the surface of said cells to be treated and a second sequence encoding a protein selected from the GILR protein and derivatives according to claim 9 or 10, that when expressed in said cells is capable of inhibiting apoptosis; and

(b) infecting said cells with said vector of (a).

18. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity if GILR proteins in said cells, comprising treating said cells with antibodies or active fragments or derivatives thereof, according to claim 14, said treating being by application of a suitable composition containing said antibodies, active fragments or derivatives thereof to said cells.

19. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity of GILR proteins in said cells, comprising treating said cells with an oligonucleotide sequence encoding an antisense sequence for at least part of the DNA sequence encoding a GILR protein according to any one of claims 1-6, said oligonucleotide sequence being capable of blocking the expression of the GILR protein.

20. Use according to claim 19 wherein said oligonucleotide sequence is introduced to said cells via a virus of claim 17 wherein said second sequence of said virus encodes said oligonucleotide sequence.

21. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for treating tumor cells or HIV-infected cells or other diseased cells, to enhance apoptosis in said cells by inhibiting the activity of GILR proteins in said cells, comprising:

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein capable of binding to a specific tumor cell surface receptor or HIV-infected cell surface receptor or receptor carried by other diseased cells and a sequence encoding an inactive GILR mutant protein, said mutant protein, when expressed in said tumor, HIV-infected, or other diseased cell is capable of inhibiting the activity of normal endogenous GILR and enhancing apoptosis in said cells; and

(b) infecting said tumor or HIV-infected cells or other diseased cells with said vector of (a).

22. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity of GILR proteins in said cells, comprising applying the ribozyme procedure in which a vector encoding a ribozyme sequence capable of interacting with a cellular mRNA sequence encoding a GILR protein according to claim 11 or 12, is introduced into said cells in a form that permits expression of said ribozyme sequence in said cells, and wherein when said ribozyme sequence is expressed in said cells it interacts with said cellular mRNA sequence and cleaves said mRNA sequence resulting in the inhibition of expression of said GILR protein in said cells.

23. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity of GILR proteins in said cells, comprising introducing into said cells a peptide that is capable of binding the normal endogenous GILR in said cells and inhibiting its activity thereby enhancing apoptosis.

24. A process for isolating and identifying proteins, according to claim 11 or 12, which are GILR-like proteins belonging to the leucine zipper family or are proteins capable of binding directly to GILR, comprising applying the yeast two-hybrid procedure in which a sequence encoding said GILR is carried by one hybrid vector and sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells and the positive transformed cells being isolated, followed by extraction of the said second hybrid vector to obtain a sequence encoding a protein which binds to said GILR.

25. The use according to any one of claims 15-23 wherein said protein is at least one of the GILR proteins and derivatives thereof.

26. A pharmaceutical composition for the inhibition of apoptosis in cells or for stimulating lymphocyte activation, comprising, as active ingredient, at least one GILR protein, according to claim 11 or 12, its biologically active derivatives or mixtures thereof.

27. A pharmaceutical composition for inhibiting apoptosis in cells or for stimulating lymphocyte activation comprising, as active ingredient, a recombinant animal virus vector encoding a protein capable of binding a cell surface receptor and encoding at least one GILR protein or derivatives according to claim 11 or 12.

28. A pharmaceutical composition for enhancing apoptosis in cells by inhibiting GILR activity in said cells, comprising as active ingredient, an oligonucleotide sequence encoding an anti-sense sequence of the GILR protein mRNA sequence according to any one of claims 1-6.

29. A pharmaceutical composition for enhancing apoptosis in cells by inhibiting GILR activity in said cells, comprising, as active ingredient, an inactive mutant GILR protein or DNA sequence encoding said inactive mutant GILR protein, which GILR mutant, when

introduced into, or expressed in, said cells inhibits the activity of the normal endogenous GILR protein.

30. A pharmaceutical composition for enhancing apoptosis in cells by inhibiting GILR activity in said cells, comprising, as active ingredient, a peptide capable of binding to the active site or the leucine zipper domain of GILR and thereby inhibiting normal endogenous GILR activity in cells.

31. A GILR protein, according to any one of claims 11 or 12, for use as a medicament.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PIERACCIOLI, Daniele
Istituto Farmacologico Serono SpA
Via Casilina, 125
I-00176 Rome
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	22.06.99
Applicant's or agent's file reference WO/348 Apparil Modulat	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/02490	27/04/1998	28/04/1997

Applicant
APPLIED RESEARCH SYSTEMS ARS HOLDING N.V et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Vullo, C Tel.(+49-89) 2399-8061

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WO/348		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
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International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V et al.		

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   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/11/1998	22.06.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Vollbach, S Telephone No. (+49-89) 2399 8715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/02490

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-70 as originally filed

Claims, No.:

1-31 as received on 14/05/1999 with letter of 11/05/1999

Drawings, sheets:

1/20-20/20 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 21-31.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 21-31 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. R asoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,6
	No:	Claims	2-5,7-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,6,16-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separat sheet

1. The present set of claims, in principle, comprises two groups of claims, namely those which are directed to the DNA sequence encoding the "GILR" protein, the corresponding protein and antibodies specific for said protein (Claims 1-14), and claims which are directed to medical uses of said protein and pharmaceutical compositions (claim 15-31).

As far as the first group is concerned, at least, in the present form, they are not new and/or inventive. In fact, the "GILR" protein which belong to the leucine zipper family" has a high degree of homology with other members of said family (see e.g. D1= J. Biol Chem, vol. 267 (15), Shibanuma et al., 1992; and D2= Biochem Biophys Res Commun, vol. 222 (3), Jay et al., 1996) respectively to proteins which are not known to belong to said family (See D3=EUR J Biochem, vol. 216 (2), Sillard et al. 1993). Therefore present claims 2-5,7-15 of said group insofar as they refer to "derivatives, parts sequences defined by the capability to hybridize to a specific DNA sequence" are not novel in view of D1-D3.
As far as the second group of claims is concerned several objections apply.
First, general applications or uses (i.e claims 15-20) cannot be regarded inventive since they are obvious in view of the known characteristics of the members of the leucine zipper family (D1-D2). Second with regard to more specific uses, it has to be mentioned that these specific uses are merely based on some preliminary results which are considered insufficient to proof that the protein indeed can be successfully applied for the indicated purposes. Therefore said claims are not sufficiently supported by experimental data in this respect, but are merely based on speculations. This clearly contravenes the requirements of Article 6 PCT.

2. Moreover, claim 15 is drafted in the form "use of protein GILR in the preparation of a medicament for inhibiting apoptosis". Most of the other claims merely refer to different forms of applying said protein or the DNA. Thus it is questionable whether said claims have any influence or relevance on the scope of "basic" claim 1.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JAY P ET AL: "Cloning of the human homologue of the TGF beta-stimulated clone 22 gene." BIOCHEM BIOPHYS RES COMMUN, MAY 24 1996, 222 (3) P821-6, XP002038877 UNITED STATES see abstract see page 823, paragraph 3; figure 1 see page 10222, left-hand column, paragraph 3 ---	1-14,31
X	KING LB ET AL: "A targeted glucocorticoid receptor antisense transgene increases thymocyte apoptosis and alters thymocyte development." IMMUNITY, NOV 1995, 3 (5) P647-56, XP002038878 UNITED STATES see the whole document ---	1,2, 7-11,13, 14,18, 28,30,31
X	BARRETT, THOMAS J. ET AL: "Coordinate Regulation of Glucocorticoid Receptor and c- jun Gene Expression Is Cell Type-Specific and Exhibits Differential Hormonal Sensitivity for Down- and Up-Regulation" BIOCHEMISTRY (1996), 35(30), 9746-9753 CODEN: BICHAW;ISSN: 0006-2960, XP002038879 see the whole document ---	1,2, 7-11, 13-15, 25,26, 30,31
A	YANG, YILI ET AL: "Fas and activation-induced Fas ligand mediate apoptosis of T cell hybridomas: inhibition of Fas ligand expression by retinoic acid and glucocorticoids" J. EXP. MED. (1995), 181(5), 1673-82 CODEN: JEMEAV;ISSN: 0022-1007, XP002038880 see the whole document ---	1,2,7-9, 13-15, 26,30,31
A	FENG, ZHIWEI ET AL: "Glucocorticoid and progesterone inhibit involution and programmed cell death in the mouse mammary gland" J. CELL BIOL. (1995), 131(4), 1095-103 CODEN: JCLBA3;ISSN: 0021-9525, XP002038881 see the whole document ---	1,2, 7-11, 13-15, 26,30,31
A	KATO, TOMOYUKI ET AL: "Inhibition by dexamethasone of human neutrophil apoptosis in vitro" NAT. IMMUN. (1996), VOLUME DATE 1995, 14(4), 198-208 CODEN: NAIMEL;ISSN: 1018-8916, XP002038882 see the whole document ---	1,2,5-9, 11-13, 24,28,29

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SILLARD R ET AL: "A novel 77-residue peptide from porcine brain contains a leucine-zipper motif and is recognized by an antiserum to delta-sleep-inducing peptide." EUR J BIOCHEM, SEP 1 1993, 216 (2) P429-36, XP002078135 GERMANY see the whole document ---	1,3-6,12
P,X	DADAMIO F ET AL: "A new dexamethasone-induced gene of the leucine zipper family protects T lymphocytes from TCR/CD3-activated cell death" IMMUNITY, 1997, 7, 803-812, XP002078136 see the whole document ---	1-31
T	JEHN BM ET AL: "Gene regulation associated with apoptosis" CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, 1997, 06-7, 179-193, XP002038883 see page 181 - page 185 see page 187 - page 189 ---	1,2, 7-11, 13-15, 26,30,31
T	OHTA S ET AL: "Mechanism of apoptotic cell death of human gastric carcinoma cells mediated by transforming growth factor beta" BIOCHEMICAL JOURNAL, 06-1997, 324, 777-782, XP002038884 see the whole document -----	1-31

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 November 1998 (30.11.98)	
International application No. PCT/EP98/02490	**Applicant's or agent's file reference** WO/348
International filing date (day/month/year) 27 April 1998 (27.04.98)	**Priority date** (day/month/year) 28 April 1997 (28.04.97)
Applicant RICCARDI, Carlo	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 November 1998 (12.11.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Athina Nickitas-Etienne
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/47, G01N 33/50, A61K 38/17, 48/00, C12N 5/10

A1

(11) International Publication Number: WO 98/49291

(43) International Publication Date: 5 November 1998 (05.11.98)

(21) International Application Number: PCT/EP98/02490

(22) International Filing Date: 27 April 1998 (27.04.98)

(30) Priority Data:
97107033.9 28 April 1997 (28.04.97) EP

(34) Countries for which the regional or international application was filed: IT et al.

(71) Applicant (for all designated States except US): APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. [NL/NL]; John B. Gorsiraweg 14, Curacao (AN).

(72) Inventor; and
(75) Inventor/Applicant (for US only): RICCARDI, Carlo [IT/IT]; Via Del Favarone, 37, I-06100 Perugia (IT).

(74) Agent: PIERACCIOLI, Daniele; Istituto Farmacologico Serono S.p.A., Via Casilina, 125, I-00176 Rome (IT).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INTRACELLULAR GLUCOCORTICOID-INDUCED LEUCINE ZIPPERS MODULATORS OF APOPTIC CELL DEATH PATHWAYS

(57) Abstract

A DNA sequence encoding a glucocorticoid-induced leucine-zipper family related protein (GILR), isoforms, fragments or analogs thereof, said GILR, isoforms, fragments or analogs thereof capable of inhibiting apoptosis and stimulating lymphocyte activity, GILR proteins, isoforms, analogs, fragments and derivatives thereof encoded by the aforesaid DNA sequence, their preparation and uses.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02490

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 G01N33/50 A61K38/17 A61K48/00
C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIBANUMA M ET AL: "Isolation of a gene encoding a putative leucine zipper structure that is induced by transforming growth factor beta 1 and other growth factors." J BIOL CHEM, MAY 25 1992, 267 (15) P10219-24, XP002038876 UNITED STATES see abstract see page 10222, left-hand column, paragraph 3; figure 5 --- -/--	1-14,31

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 1998	01/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gurdjian, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	FENG, ZHIWEI ET AL: "Glucocorticoid and progesterone inhibit involution and programmed cell death in the mouse mammary gland" J. CELL BIOL. (1995), 131(4), 1095-103 CODEN: JCLBA3;ISSN: 0021-9525, XP002038881 see the whole document ---	1,2, 7-11, 13-15, 26,30,31
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P,X	DADAMIO F ET AL: "A new dexamethasone-induced gene of the leucine zipper family protects T lymphocytes from TCR/CD3-activated cell death" IMMUNITY, 1997, 7, 803-812, XP002078136 see the whole document ---	1-31
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
WO/348		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 02490	27/04/1998	28/04/1997

Applicant

APPLIED RESEARCH SYSTEMS ARS HOLDING N.V et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   INTRACELLULAR GLUCOCORTICOID-INDUCED LEUCINE ZIPPERS MODULATORS OF APOPTIC CELL DEATH PATHWAYS

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 1998	01/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gurdjian, D

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Replaced by Clm 34

CLAIMS

1. A DNA sequence encoding a glucocorticoid-induced leucine-zipper family related protein (GILR), isoforms, fragments or analogs thereof, said GILR, isoforms, fragments or analogs thereof capable of inhibiting apoptosis and stimulating lymphocyte activity.

2. A DNA sequence according to claim 1 selected from the group consisting of :

(a) a cDNA sequence derived from the coding region of a native GILR protein;

(b) DNA sequences capable of hybridization to a sequence of (a) under moderately stringent conditions and which encode a biologically active GILR protein; and

(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (a) and (b) and which encode a biologically active GILR protein.

3. A DNA sequence according to claim 1 or claim 2 comprising at least part of the DNA sequence SEQ ID NO: 1 and encoding at least one active GILR protein, isoform, analog or fragment

4. A DNA sequence according to claim 3 encoding a GILR protein, isoform, analog or fragment having at least part of the amino acid sequence SEQ ID NO: 2.

5. A DNA sequence according to claim 1 or claim 2 comprising at least part of the DNA sequence SEQ ID NO: 5 and encoding at least one active human GILR protein, isoform, analog or fragment.

6. A DNA sequence according to claim 5 encoding a human GILR protein, isoform, analog or fragment having at least part of the amino acid sequence SEQ ID NO: 6.

7. A vector comprising a DNA sequence according to any one of claims 1-6.

8. A vector according to claim 7 capable of being expressed in a eukaryotic host cell.

9. A vector according to claim 7 capable of being expressed in a prokaryotic host cell.

10. Transformed eukaryotic or prokaryotic host cells containing a vector according to any one of claims 7-9.

11. A GILR protein, isoform, fragment, functional analogs or derivatives thereof encoded by a DNA sequence according to any one of claims 1-6, said protein, isoform, fragment, analogs and derivatives thereof being capable of inhibiting apoptosis and stimulating lymphocyte activity.

12. A GILR protein, isoform, fragment, analogs and derivatives thereof according to claim 11, wherein said protein, isoform, analogs, fragments and derivatives have at least part of the amino acid sequence SEQ ID NO: 2 or of the amino acid sequence SEQ ID NO: 5.

13. Process for the preparation the GILR protein, isoform, fragment, analogs or derivatives thereof according to claim 11 or 12, comprising growing the transformed host cells according to claim 12 under conditions suitable for the expression of said protein, analogs or derivatives, effecting post-translational modifications as necessary for obtaining of said protein, fragments, analogs or derivatives and isolating said expressed protein, fragments, analogs or derivatives.

14. Antibodies or active fragments or derivatives thereof, specific for the GILR protein, isoform, fragment, analogs or derivatives according to claim 11 or 12.

15. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for the inhibition of apoptosis in cells, mediated by the Fas/FasL system, CD3/TCR system or other intracellular mediators of apoptosis, comprising treating said cells with one or more GILR proteins, isoforms, analogs, fragments or derivatives

according to claim 11 or 12, wherein said treating of said cells comprises introducing into said cells said one or more proteins, isoforms, analogs, fragments or derivatives in a form suitable for intracellular introduction thereof, or introducing into said cells a DNA sequence encoding said one or more proteins, isoforms, analogs, fragments or derivatives in the form of a suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.

16. Use according to claim 15, wherein said treating of cells comprises introducing into said cells a DNA sequence encoding said GILR protein, isoforms, analogs, fragments or derivatives in the form of a suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.

17. Use according to claim 15 or 16 wherein said treating of said cells is by transfection of said cells with a recombinant animal virus vector comprising the steps of:

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein (ligand) that is capable of binding to a specific cell surface receptor on the surface of said cells to be treated and a second sequence encoding a protein selected from the GILR protein, isoforms, analogs, fragments and derivatives according to claim 9 or 10, that when expressed in said cells is capable of inhibiting apoptosis; and

(b) infecting said cells with said vector of (a).

18. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity if GILR proteins in said cells, comprising treating said cells with antibodies or active fragments or derivatives thereof, according to claim 14, said treating being by application of a suitable composition containing said antibodies, active fragments or derivatives thereof to said cells.

19. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity of GILR proteins in said cells, comprising treating said cells with an oligonucleotide sequence encoding an antisense sequence for at least part of the DNA sequence encoding a GILR protein according to any one of claims 1-6, said oligonucleotide sequence being capable of blocking the expression of the GILR protein.

20. Use according to claim 19 wherein said oligonucleotide sequence is introduced to said cells via a virus of claim 17 wherein said second sequence of said virus encodes said oligonucleotide sequence.

21. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for treating tumor cells or HIV-infected cells or other diseased cells, to enhance apoptosis in said cells by inhibiting the activity of GILR proteins in said cells, comprising:

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein capable of binding to a specific tumor cell surface receptor or HIV-infected cell surface receptor or receptor carried by other diseased cells and a sequence encoding an inactive GILR mutant protein, said mutant protein, when expressed in said tumor, HIV-infected, or other diseased cell is capable of inhibiting the activity of normal endogenous GILR and enhancing apoptosis in said cells; and

(b) infecting said tumor or HIV-infected cells or other diseased cells with said vector of (a).

22. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity of GILR proteins in said cells, comprising applying the ribozyme procedure in which a vector encoding a ribozyme sequence capable of interacting with a cellular mRNA sequence encoding a GILR protein according to claim 11 or 12, is introduced into said cells in a form that permits expression of said ribozyme sequence in said cells, and wherein when said ribozyme sequence is expressed in said cells it interacts with said cellular mRNA

sequence and cleaves said mRNA sequence resulting in the inhibition of expression of said GILR protein in said cells.

23. Use of a GILR protein according to claim 11 or 12 in the manufacture of a medicament for enhancing apoptosis in cells by inhibiting the activity of GILR proteins in said cells, comprising introducing into said cells a peptide that is capable of binding the normal endogenous GILR in said cells and inhibiting its activity thereby enhancing apoptosis.

24. A process for isolating and identifying proteins, according to claim 11 or 12, which are GILR-like proteins belonging to the leucine zipper family or are proteins capable of binding directly to GILR, comprising applying the yeast two-hybrid procedure in which a sequence encoding said GILR is carried by one hybrid vector and sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells and the positive transformed cells being isolated, followed by extraction of the said second hybrid vector to obtain a sequence encoding a protein which binds to said GILR.

25. The use according to any one of claims 15-23 wherein said protein is at least one of the GILR isoforms, analogs, fragments and derivatives thereof.

26. A pharmaceutical composition for the inhibition of apoptosis in cells or for stimulating lymphocyte activation, comprising, as active ingredient, at least one GILR protein, according to claim 11 or 12, its biologically active fragments, analogs, derivatives or mixtures thereof.

27. A pharmaceutical composition for inhibiting apoptosis in cells or for stimulating lymphocyte activation comprising, as active ingredient, a recombinant animal virus vector encoding a protein capable of binding a cell surface receptor and encoding at least one GILR protein, isoform, active fragments or analogs, according to claim 11 or 12.

28. A pharmaceutical composition for enhancing apoptosis in cells by inhibiting GILR activity in said cells, comprising as active ingredient, an oligonucleotide sequence encoding an anti-sense sequence of the GILR protein mRNA sequence according to any one of claims 1-6.

29. A pharmaceutical composition for enhancing apoptosis in cells by inhibiting GILR activity in said cells, comprising, as active ingredient, an inactive mutant GILR protein or DNA sequence encoding said inactive mutant GILR protein, which GILR mutant, when introduced into, or expressed in, said cells inhibits the activity of the normal endogenous GILR protein.

30. A pharmaceutical composition for enhancing apoptosis in cells by inhibiting GILR activity in said cells, comprising, as active ingredient, a peptide capable of binding to the active site or the leucine zipper domain of GILR and thereby inhibiting normal endogenous GILR activity in cells.

31. A GILR protein, according to any one of claims 11 or 12, for use as a medicament.

ABSTRACT

A DNA sequence encoding a glucocorticoid-induced leucine-zipper family related protein (GILR), isoforms, fragments or analogs thereof, said GILR, isoforms, fragments or analogs thereof capable of inhibiting apoptosis and stimulating lymphocyte activity, GILR proteins, isoforms, analogs, fragments and derivatives thereof encoded by the aforesaid DNA sequence, their preparation and uses.